

Sapphire News

Addressing Nonlinearity in the Exposure-Response Relationship for a Genotoxic Carcinogen: Cancer Potency Estimates for Ethylene Oxide.

Kirman CR, Sweeney LM, Teta MJ, Sielken RL, Valdez-Flores C, Albertini RJ, Gargas ML.

Ethylene oxide (EO) has been identified as a carcinogen in laboratory animals. Although the precise mechanism of action is not known, tumors in animals exposed to EO are presumed to result from its genotoxicity. The overall weight of evidence for carcinogenicity from a large body of epidemiological data in the published literature remains limited. There is some evidence for an association between EO exposure and lympho/hematopoietic cancer mortality. Of these cancers, the evidence provided by two large cohorts with the longest follow-up is most consistent for leukemia. Together with what is known about human leukemia and EO at the molecular level, there is a body of evidence that supports a plausible mode of action for EO as a potential leukemogen. Based on a consideration of the mode of action, the events leading from EO exposure to the development of leukemia (and therefore risk) are expected to be proportional to the square of the dose. In support of this hypothesis, a quadratic dose-response model provided the best overall fit to the epidemiology data in the range of observation. Cancer dose-response assessments based on human and animal data are presented using three different assumptions for extrapolating to low doses: (1) risk is linearly proportionate to dose; (2) there is no appreciable risk at low doses (margin-of-exposure or reference dose approach); and (3) risk below the point of departure continues to be proportionate to the square of the dose. The weight of evidence for EO supports the use of a nonlinear assessment. Therefore, exposures to concentrations below 37 $\mu\text{g}/\text{m}^3$ are not likely to pose an appreciable risk of leukemia in human populations. However, if quantitative estimates of risk at low doses are desired and the mode of action for EO is considered, these risks are best quantified using the quadratic estimates of cancer potency, which are approximately 3.2- to 32-fold lower, using alternative points of departure, than the linear estimates of cancer potency for EO. An approach is described for linking the selection of an appropriate point of departure to the confidence in the proposed mode of action. Despite high confidence in the proposed mode of action, a small linear component for the dose-response relationship at low concentrations cannot be ruled out conclusively. Accordingly, a unit risk value of 4.5×10^{-8} ($\mu\text{g}/\text{m}^3$)⁻¹ was derived for EO, with a range of unit risk values of 1.4×10^{-8} to 1.4×10^{-7} ($\mu\text{g}/\text{m}^3$)⁻¹ reflecting the uncertainty associated with a theoretical linear term at low concentrations.